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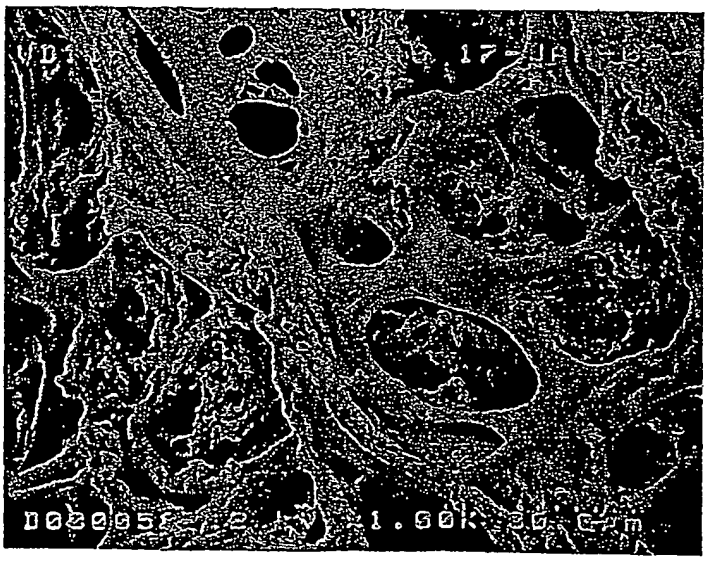
(54) Title: CO-CONTINUOUS PHASE COMPOSITE POLYMER BLENDS FOR IN-VIVO AND IN-VITRO BIOMEDICAL APPLICATIONS



(57) Abstract: Tissue-compatible polymer composites characterized by a co-continuous, integrated multi-phase, three-dimensional microstructured network of two or more immiscible biocompatible polymers.

WO 03/103925 A1

CO-CONTINUOUS PHASE COMPOSITE POLYMER BLENDS FOR IN-VIVO AND IN-VITRO BIOMEDICAL APPLICATIONS

CROSS REFERENCE TO RELATED APPLICATION

The present application claims priority benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application Serial No. 60/385,883 filed June 6, 2002, the disclosure of which is incorporated by reference.

BACKGROUND OF THE INVENTION

Materials used for human implants and tissue growth scaffolding require several key properties that include sufficient strength and toughness, compatibility with tissue environments, biochemical durability, avoiding release of moieties that stimulate body rejection mechanisms; and proper surface characteristics to promote adhesion of adjacent tissue. The compatibility of the implant or scaffolding with specific types of tissue is particularly important with regard to induction of tissue growth and conductive growth regimes to produce viable tissue development in-vivo.

This direction has led to the evaluation of numerous types of porous scaffolding structures made from inorganic biocompatible materials such as hydroxyapatite and various polymers. The functionality of hydroxyapatite type materials is principally derived from the biochemical similarity of this material with the inorganic phase of bone tissue. The functionality of the porous polymer materials fall into three distinct categories: [1] materials that are passive in vivo, [2] materials that degrade in vivo and produce benign or growth promoting degradation products, and [3] materials that can be doped with drugs and other biochemical agents that promote growth, reduce inflammation or generate other desirable tissue characteristics in-vivo.

However, mechanical and biochemical compatibilization of the implant structure with the body environment continues to be a key issue in implant development. Overall the ideal

by selecting the volume ratio of the two blend components to approximately equal the viscosity ratio.

Based on experimental observations that the phase with the lower viscosity or the higher volume fraction, tended to form the continuous phase, Jordhamo et al, *Polym. Eng. Sci., 26(8)*, 517 (1986), suggested a semi-empirical expression which relates the region of expected dual phase co-continuity to the viscosity ratio and volume ratio of the blend components. Their paper asserts that the condition of dual phase co-continuity can be achieved by the application of shear to a polymer blend system close to the phase inversion region. As described by Equation (1), the model predicts that phase inversion should occur when the viscosity ratio and the volume ratio are about equal, i.e., when

$$\frac{V_A}{V_B} \approx \frac{\eta_A}{\eta_B} \qquad (1)$$

wherein η_i is the viscosity of phase i and V_i is the volume fraction of phase i. As can be seen, the model sets the viscosity ratio as being approximately equal to the volumetric ratio. The material described in U.S. Patent No. 5,298,214 exhibits this two-phase microstructure. One phase consists essentially of polystyrene and the other consists essentially of polyolefin.

Unfortunately, biomedical implants cannot be made from waste plastic recycling streams. Furthermore, while the co-continuous polymer phases of U.S. Patent No. 5,298,214 form three-dimensional integrated interpenetrating networks, there is no disclosure regarding how either phase can at least in part be removed or otherwise replaced with a three dimensional interpenetrating network of pores to form a structure suitable for biomedical implantation.

SUMMARY OF THE INVENTION

It has now been discovered that immiscible tissue-compatible polymer combinations will form co-continuous, composite multi-phase, three-dimensional integrated interpenetrating micro-structure networks when blended and formed according to the process described by U.S. Patent No. 5,298,214, and, furthermore, because such polymers can be selected to

composite structure by contacting the composite with aqueous solutions of the type employed for in vitro testing of polymer bioerodibility under conditions essentially similar to in vitro testing. Alternately, at least one polymer can be removed by contact with a solvent for the polymer.

Therefore, according to another aspect of the present invention, a porous tissue-compatible polymer structure is provided having a three-dimensional microstructured porous network. When the polymer structure begins with more than two polymers, and more than one remain after one or more are removed, the polymer portion of the structure is a co-continuous, integrated multi-phase, three-dimensional microstructured network of two or more immiscible biocompatible polymers.

Porous composites according to this aspect of the present invention may have at least one polymer phase completely or partially removed in vitro to create a full or partial network of pores for tissue ingrowth. There is no lower limit on the amount of polymer phase removed because even the slightest removal of polymer will create a composite with a textured surface that promotes tissue adhesion.

Thus, according to another aspect of the present invention, a method is provided for forming porous tissue compatible polymer structures having three-dimensional microstructured porous networks, including the steps of providing a tissue-compatible polymer composite having a co-continuous, integrated multi-phase, three-dimensional microstructured network of two or more immiscible biocompatible polymers, at least one of which is bioerodible, and dissolving in vitro at least a portion of a bioerodible polymer.

The polymer composites of the present invention, with or without porous networks formed in vitro, can be fabricated into medical implant devices by essentially conventional means. Therefore, another aspect of the present invention provides biocompatible medical implant devices formed from the polymers of the present invention. Medical implant device include porous polymer scaffolds for tissue engineering and tissue-guided regeneration applications.

FIG. 5 depicts the etched composite of FIG.2 at 300X viewed perpendicular to the extrusion axis;

FIG. 6 depicts the etched composite of FIG.2 at 1300X viewed perpendicular to the extrusion axis;

FIG. 7 depicts the results of a PBS aging study for a PMMA/PLA composite material of the present invention;

FIG.8 depicts the results of a PBS aging study for another PMMA/PLA composite material of the present invention;

FIG. 9 the results of a deionized water aging study for the PMMA/PLA composite material of FIG. 8; and

FIG. 10 depicts a comparison of modulus values averaged over time for polymer composites of the present invention and unblended polymers.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The tissue compatible composites are prepared using the co-continuous polymer blend technology disclosed by U.S. Patent No. 5,298,214. Prior experience with other polymer systems, particularly the polystyrene/high density polyethylene system, has revealed that co-continuous composites can be produced from immiscible polymers by melt processing. The key feature needed to achieve these composites is proper composition percentages plus high shear melt processing, such as that encountered with proper screw configuration and machine operation in melt extrusion and injection molding. The application of the technology to immiscible tissue compatible polymers is essentially conventional. The invention resides in the recognition that such polymers can be processed using this technology to form biocompatible composite materials, and the unique and unexpected properties resulting possessed by the composite materials.

according to the present invention, while other of the two polymers may be the slower dissolving component in a different composite according to the present invention.

The composite is formed by blending two or more immiscible polymers. The term immiscible, synonymous with non-miscible, is used in its ordinary sense with respect to the polymers as defined by Billmeyer, Textbook of Polymer Science (3rd Ed., John Wyley & Sons, 1984). One of ordinary skill in the art can easily select two or more immiscible polymers for processing without undue experimentation. For example low water solubility polymers, or water-insoluble polymers can be used as the phase that dissolves more slowly or not at all, and water soluble polymers can be employed for phases that are intended to dissolve. Combinations of water soluble polymers with polymers that are water insoluble or have lower water solubility are generally good candidates because these materials will usually be non-miscible.

The proper composition ratio of two (or more) constituent polymers is defined by the simple ratio given in Equation (1) that requires only rheological characterization of the polymers over the thermal processing range of the extruder or injection molder. Eliminating V_B by the relationship $V_A + V_B = 1$, it becomes directly apparent that if the viscosity ratio is 0.5, for example, the volume fraction of the more fluid component should be one-third. A range of co-continuous regions exists and is centered on or near the predicted composition as shown qualitatively in Figure 1 for an A-B polymer mixture. A wide range of polymer molecular weights can be used to obtain a range of performance. Component ratios will vary depending upon the viscosity and volume fraction for the molecular weights of the polymers selected. The component weight ratios of co-continuous regions will typically range between about 15:85 and about 85:15, preferably between about 25:75 and about 75:25, and more preferably between about 30:70 and about 70:30%.

Porous polymer composites can be prepared in vitro, as discussed above, by removing at least one polymer phase from a polymer composite of the present invention. In addition to promoting tissue ingrowth, porosity also increases the surface area of the biorerodible polymer when it is in contact with the organic fluids of the body, thereby increasing the rate of bioerosion. Alternately, porosity may be introduced by foaming one or more polymer

Blends will contain both PMMA and PLA, PGA and/or copolymers thereof as co-continuous phases. The PMMA will be the structural phase that provides the necessary strength to the structure and PLA, PGA, and/or copolymers thereof provide a slowly soluble biodegradable phase that produces an evolving osteoinductive/conductive morphology. In addition to engineering the biochemical environment as the PLA and/or PGA dissolves to nutritionalize the surrounding tissues to stimulate ingrowth, the two-phase structure imparts increased toughness to the implant structure and the porosity generated by the dissolution of the PLA and/or PGA phase promotes adhesion sites for adjacent bone, muscle, or ligament tissue.

One of the special features of this polymer system is the similarity of solubility parameters for PMMA and PLA and PGA polymers and copolymers. Although actual values vary and depend on specific molecular weights and compositions, the solubility parameters are usually on the verge of immiscibility/miscibility. This borderline immiscibility and the processing of these two polymers in a manner that generates a co-continuous distribution of both polymers is a key feature of this embodiment of the present invention and enables several key properties. The near miscibility of the two phases enables the formation of much stronger interfacial bonds that would be possible in fully immiscible systems. Furthermore, the processing of these polymers into a co-continuous distribution maximizes the interfacial surface area, enhances the interaction between the two polymers, and enables a continuous inductive/conductive tissue growth channel to develop when the PLA, PGA and/or copolymer thereof is removed by biochemical action. In addition, if a material is desired that has minimal or no biodegradation, i.e. where tissue growth is unlikely and long term mechanical properties must be retained, the PMMA and PLA/PGA polymers can be processed to produce a miscible alloy that inhibits or greatly reduces selective degradation and channel formation.

The use of PMMA in polymer composites is also advantageous because it promotes the fastening of the composite to bone or other tissues with super glue-type adhesives better than almost any other implant material, because such adhesives are based on PMMA and related polyacrylates.

The polymer composites are shaped into articles for tissue engineering and tissue guided regeneration applications, including reconstructive surgery. The evolving porous structure allows generous cellular ingrowth, eliminating the need for cellular preseeding. The polymer composites may also be molded to form external scaffolding for the support of *in vitro* culturing of specialized cells and tissues for the creation of external support organs. The scaffold functions to mimic the extracellular matrices (ECM) of the body. The scaffold serves as both a physical support and an adhesive substrate for isolated cells during *in vitro* culture and subsequent implantation. As the transplanted cell populations grow and the cells function normally, they begin to secrete their own ECM support. The scaffold polymer is selected to degrade as the need for an artificial support diminishes.

In the reconstruction of structural tissues like cartilage and bone, tissue shape is integral to function, requiring the molding of the scaffold into articles of varying thickness and shape. Any crevices, apertures or refinements desired in the three-dimensional structure can be created by removing portions of the composite with scissors, a scalpel, a laser beam or any other cutting instrument. A fabrication sequence may be employed that involves producing large quantities of polymer composite to meet a specific end use, wherein the final shape of the implant or other component is determined by tomography and is stored in a CAD/CAM image file. The image file is then sent to a CNC (computer numerical controlled) milling machine that produces a net shape part to exact specifications

Scaffold applications include the regeneration of tissues such as nervous, musculoskeletal, cartilaginous, tendenous, hepatic, pancreatic, ocular, integumenary, arteriovenous, urinary or any other tissue forming solid or hollow organs.

The scaffold may also be used in transplantation as a matrix for dissociated cells such as chondrocytes or hepatocytes to create a three-dimensional tissue or organ. Any type of cell can be added to the scaffold for culturing and possible implantation, including cells of the muscular and skeletal systems, such as chondrocytes, fibroblasts, muscle cells and osteocytes, parenchymal cells such as hepatocytes, pancreatic cells (including Islet cells), cells of intestinal origin, and other cells such as nerve cells and skin cells, either as obtained from donors, from established cell culture lines, or even before or after genetic engineering, and

Note: Inherent Viscosity from Boerhinger Specification Sheets; value for L210 is the average value [3.4,4.4]. Constants K and a from Boehringer Spec: Fischer, Stenzel, Wegner, Kolloid-Z. and Z. Pol. 251.980 (1973). Approximation used: Intrinsic Viscosity = Inherent Viscosity

Table 2

Approximate Physical Properties for PLA 2075 and PLA 210

Property	Value
Tensile strength at 37°, 50 mm/min [MPa]	82.5
Strain at yield at 37°, 50 mm/min [%]	3.6
Young's Modulus, E, at 37° [MPa]	670
Flexural Strength, at 37°, 50 mm/min [MPa]	118
Notched Impact Strength at 37°, [J]	0.41
MFI [g/10 min]	2.7
Drying temperature	140
Minimum drying time, [h]	4
Ideal drying time, [h]	8
Glass transition, Tg	57
Crystallization Temperature, TX	180
Mark-Houwing Constants	K=1.29 x 10-4
	a. = 0.82
Density at 22° [g/cm 3]	1.256

For the PLA(L207S)/PMMA composites, the viscosity of the PMMA at 200° is 3989 and the viscosity of the PLA is 1563 Pa's, yielding a volume fraction of PLA of 28.2% as the center of the co-continuous region. Similarly, for the PLA(L210)/PMMA composites, the viscosity of the PMMA at 200° is 3989 and the viscosity of the PLA is 3739 Pa's, yielding a volume fraction of PLA of 48.4% as the center of the co-continuous region. Thus, a broad areas of the PMMA/PLA composition space is related to the current invention. Since small amounts of PLA in a largely PMMA matrix are of limited interest, the most relevant range of composition space in this system is from 15% PLA to 85% PLA, more preferably from 25 to 70% PLA, and mostpreferably from 30 - 60% PLA by volume.

system that enables a wide range of biological performance to be engineered by simply altering the composition and molecular weight of the PLA and by altering the composite composition and processing conditions.

Structure. One of the most striking features of these materials is the apparent two-phase structure that is observed in compositions processed in the co-continuous range. As shown in the photomicrographs(FIGS 2 - 6) of a 64/36% PMMA/PLA composite that was etched (dimethyl formate, 15 seconds, 25° C) to reveal the microstructure, the resulting materials are clearly co-continuous. The degradable phase, PLA, has been removed and the remaining PMMA phase clearly illustrates the desirable conductive channels. Figures 2 -4 illustrate the morphology as viewed parallel to the extrusion axis and Figure 5 - 6 illustrate the fibrous/channel structure as viewed perpendicular to the extrusion axis.

Properties

Phosphate buffer solutions aging. Small bars were cut from some of the materials produced so that they could be aged at 37° in a phosphate buffer solution that provides an approximation of in vivo conditions. The goal of this testing was to demonstrate the ability of PLA-PMMA co-continuous composites to retain modulus over a two month period. The solubility of PLA in vivo is well known and is the basis for its current use at dissolvable sutures, among other uses. By combining it with PMMA in a co-continuous structure, the PLA tissue compatibility properties can be employed while at the same time slowing the rate at which modulus is lost due to dissolution. FIGS. 7-10 show good retention of modulus over the 65-day test period.

The present invention thus provides highly biosensitive structures that simulate in-vivo conditions for promoting cellular growth and tissue repair. The foregoing examples and description of the preferred embodiment should be taken as illustrating, rather than as limiting, the present invention as defined by the claims. As would readily be appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. Such variations are not regarded as a departure from the spirit and scope of the invention, and all such variations are intended to be included within the scope of the following claims.

10. The polymer composite of claim 9, wherein at least one polymer phase comprises particles of hydroxyapatite or tricalcium phosphate.

11. The polymer composite of claim 1, wherein at least one polymer phase comprises one or more nutrient or pharmaceutical substances.

12. The polymer composite of claim 1, wherein at least one polymer phase is foamed.

13. A porous tissue-compatible polymer structure comprising a three-dimensional microstructured porous network.

14. The porous polymer structure of claim 13, wherein the polymer portion of the structure is a co-continuous, integrated multi-phase, three-dimensional microstructured network of two or more immiscible biocompatible polymers.

15. The porous polymer structure of claim 14, wherein said polymer portion comprises first and second polymer components, wherein said second polymer component is bioerodible.

16. The porous polymer structure of claim 15, wherein said first polymer component is bioerodible and erodes at a rate slower than said second polymer component.

17. The porous polymer structure of claim 15, wherein said first polymer component is PMMA and said second polymer component is selected from the group consisting of PLA, PGA and copolymers thereof.

18. The porous polymer structure of claim 13, wherein the polymer component of said structure comprises one or more substances or particles that promote bone or tissue ingrowth.

Figure 1

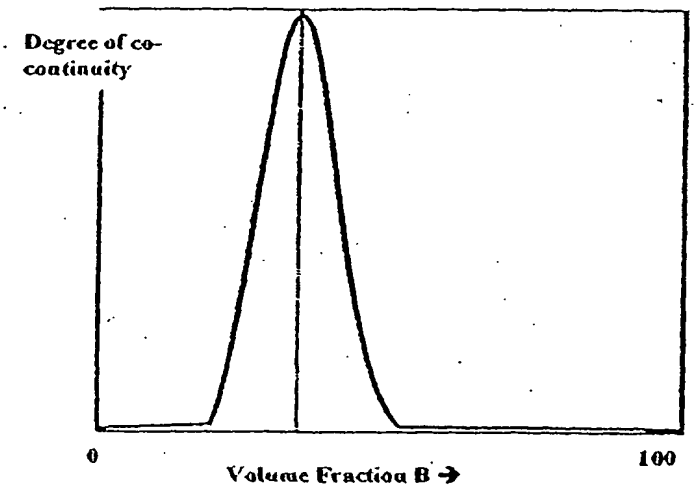


Figure 2

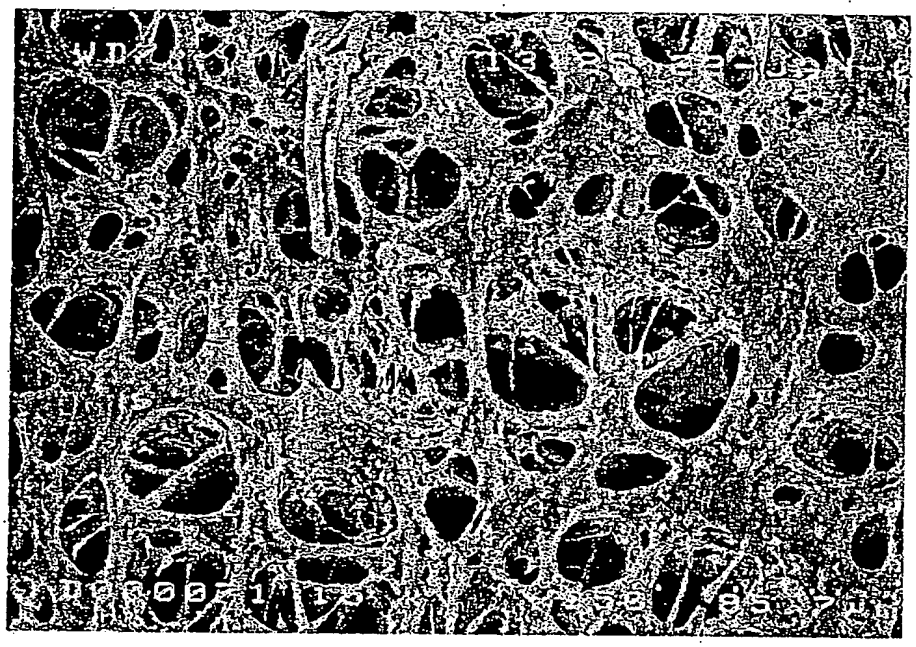
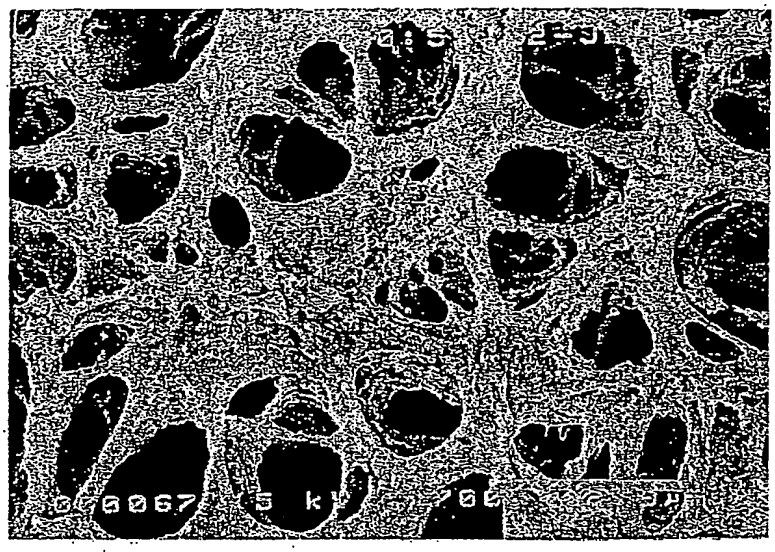


Figure 3



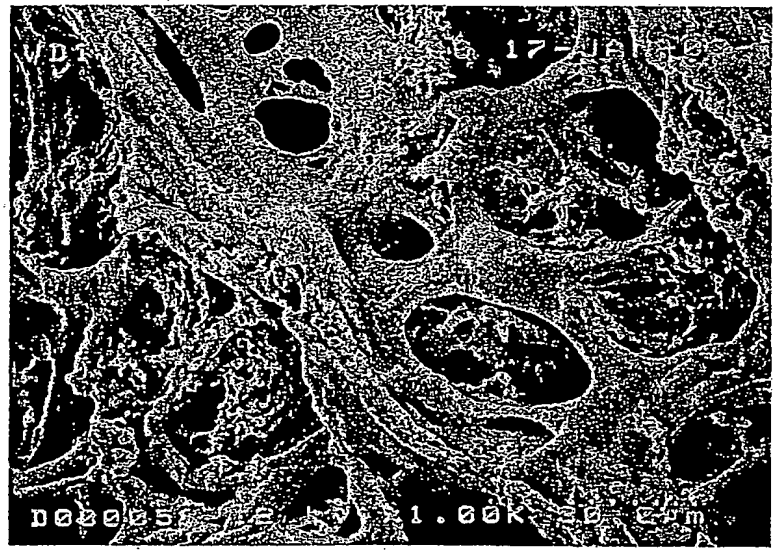
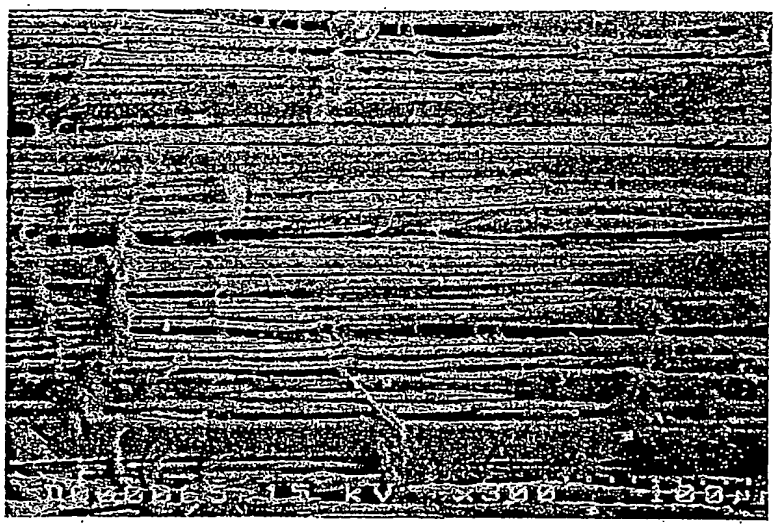


Figure 4

Figure 5



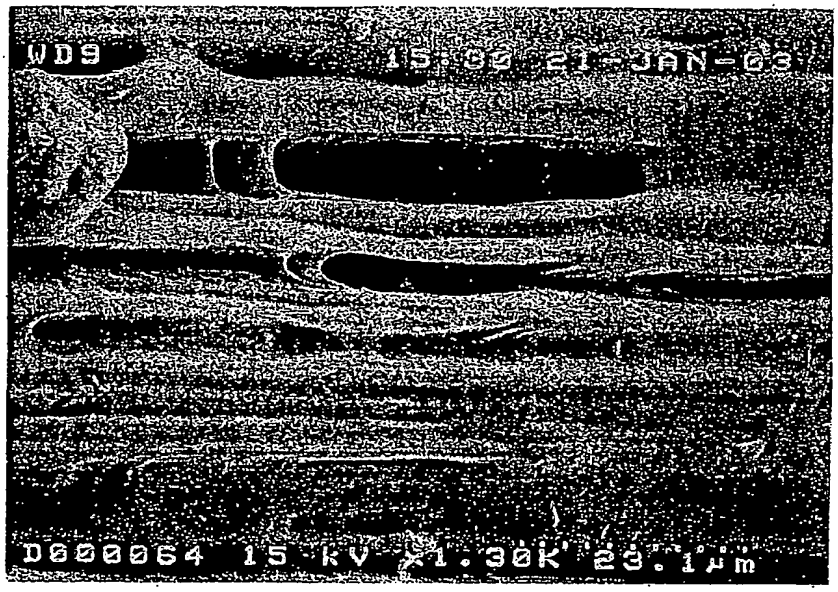
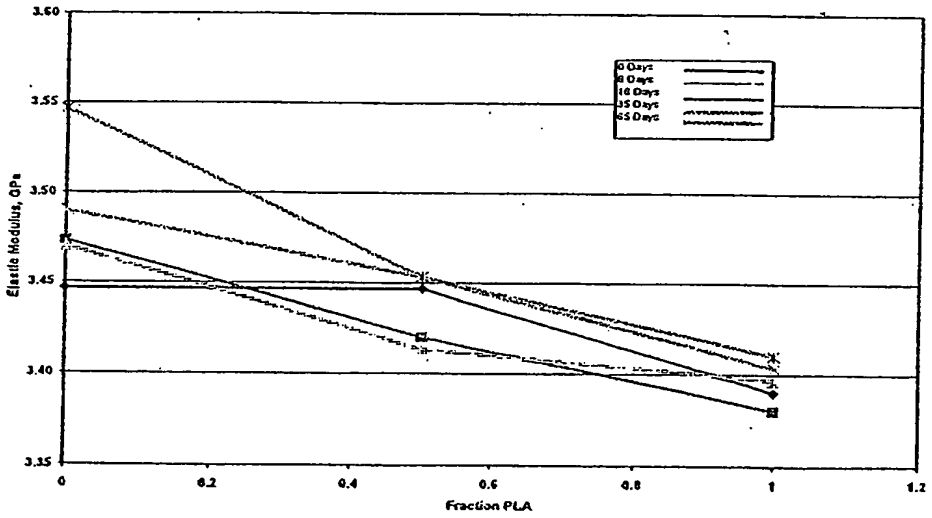


Figure 6

Figure 7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3.55
3.50
3.45
3.40
3.35
Elastic Modulus, GPa
0
0.2
0.4
0.6
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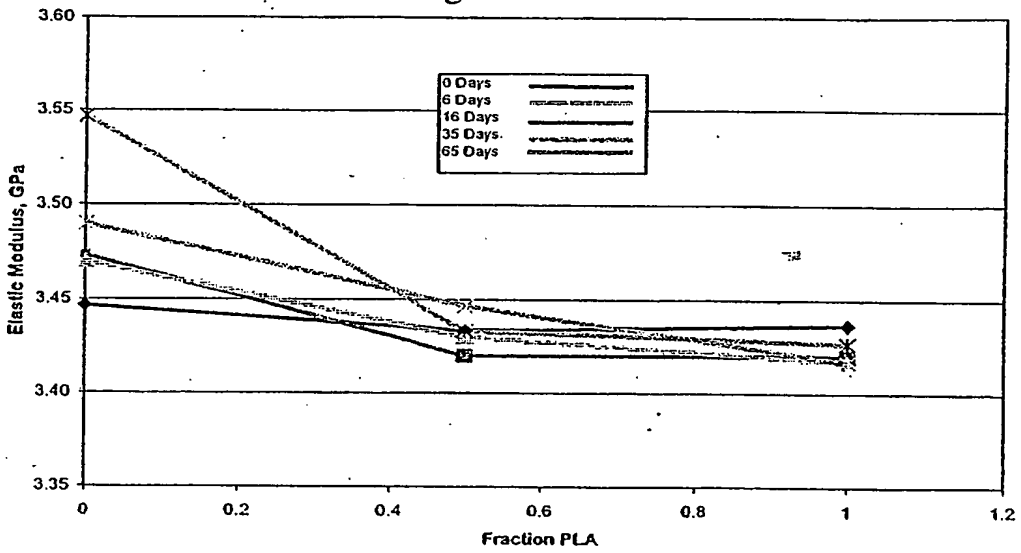
1.2
Fraction PLA
0 Days
14 Days
28 Days
35 Days
65 Days

Figure 8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Fraction PLA
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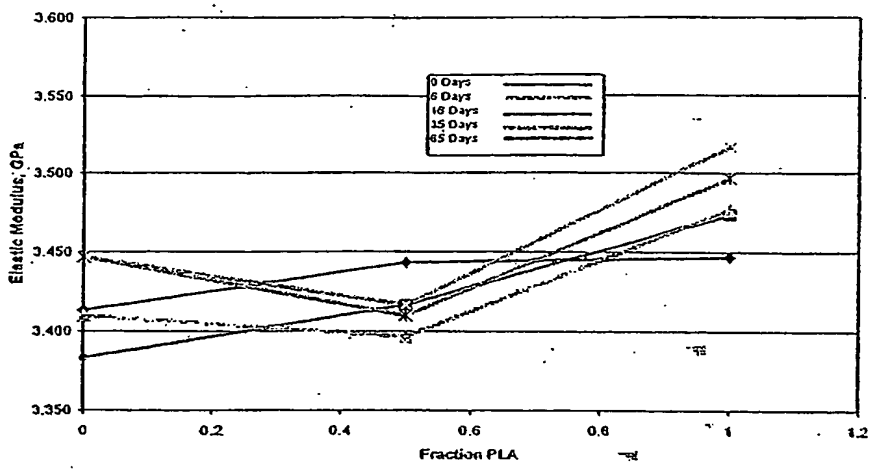
6 Days
16 Days
35 Days.
65 Days

Figure 9



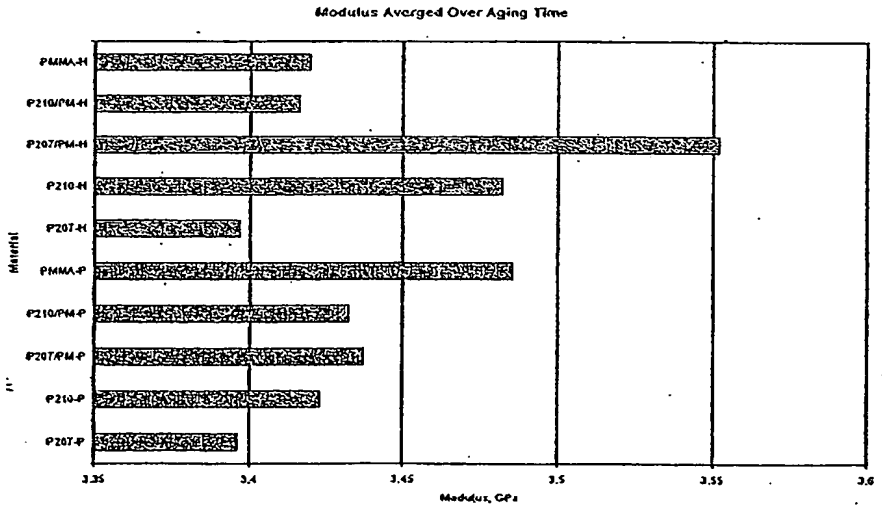


Figure 10